Metal Complexes of Benzodiazepines. Part 2.[1] The Reaction of 1,4-Benzodiazepines with Halide-bridged Complexes of Palladium(II) $[Pd_2X_4(PPr^n_3)_2]$ (X = Cl or I)*

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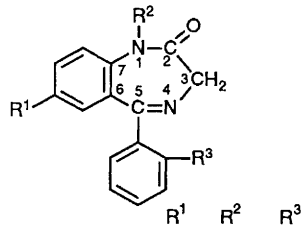
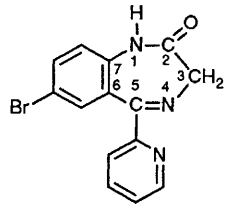
1,4-Benzodiazepines cleave the halide-bridged complexes $[Pd_2X_4(PPr^n_3)_2]$ (X = Cl or I) to give monomeric complexes in which the benzodiazepine is presumably co-ordinated through N(4) of the heterocyclic ring. The reaction between $[Pd_2I_4(PPr^n_3)_2]$ and 7-chloro-1,3-dihydro-1-methyl-5-phenyl-, 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-, 1,3-dihydro-7-nitro-5-phenyl-, and 7-bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepin-2-one and 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepine has been studied kinetically and thermodynamically in $CHCl_3$. The stability of the monomeric complexes formed varies considerably throughout the series of ligands and is much lower when the benzodiazepine is in the 2-keto form. The nucleophilic activities of these substances, as expressed by the second-order rate constants k_2 corresponding to direct attack at palladium in the cleavage reaction, are similar but much lower, for steric reasons, than that of pyridine. The difference in stability of the various complexes is attributed mainly to the difference in the rate constants corresponding to the reverse reaction, *i.e.* the release of the co-ordinated ligand.

The continuing interest in the chemistry of benzodiazepines,[2,3] the most powerful and versatile psychotherapeutic agents on the market, has prompted in the last ten years various investigations[1,4–8] on the behaviour of these substances as ligands toward metal ions. The changes induced in a benzodiazepine molecule by complexation may in fact be reflected to the pharmacological properties of the substance and therefore such studies may help in elucidating the relationship between the chemical and pharmacological properties of these drugs. So far, complexes of copper(II),[4] gold(I)[5] and gold(III),[5] mercury(II),[6] platinum(II)[7] and palladium(II)[8] have been characterized unambiguously. Although complexation generally involves N(4) of the heterocyclic ring, several co-ordination modes are possible: with palladium(II)[8,9] and platinum(II)[10] for instance adducts as well as metallated species have been obtained, while with gold(I) co-ordination through deprotonated N(1) has been reported.[5] On the whole co-ordination does not bring major changes in the ligand which retains in the complex its boat configuration. Nonetheless, apart from such studies of the synthesis and characterization of complexes of benzodiazepines, until now there has been no systematic study of the co-ordination chemistry of these ligands as far as their co-ordinating ability as well as their nucleophilic reactivity is concerned.

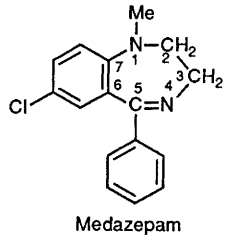
We have studied thermodynamically and kinetically the reactions between the complex *trans*-di-μ-iodo-diiodobis(tri-*n*-propylphosphine)dipalladium(II) $[Pd_2I_4(PPr^n_3)_2]$ and five 1,4-benzodiazepines which are among the most commonly marketed drugs of this class. In this paper we report the thermodynamic parameters and the equilibrium and forward rate constants, at 25 °C, in $CHCl_3$, for the reactions of $[Pd_2I_4(PPr^n_3)_2]$ with 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (diazepam), 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one (clonazepam), 1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (nitrazepam), 7-bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepin-2-one (bromazepam) and 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepine (medazepam). Furthermore, in order to make a comparison with known nucleophiles, we have studied the reaction of the same complex with pyridine and 2,6-dimethylpyridine.



	R^1	R^2	R^3
Diazepam	Cl	Me	H
Nitrazepam	NO_2	H	H
Clonazepam	NO_2	H	Cl



Bromazepam

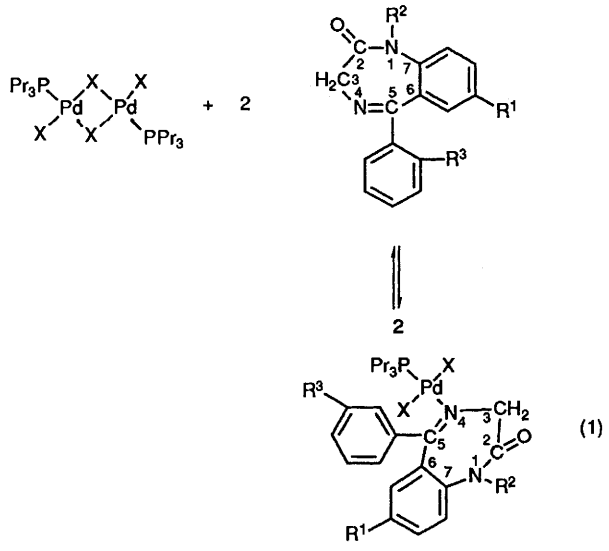


Medazepam

Experimental

The complexes $[Pd_2X_4(PPr^n_3)_2]$ were prepared, according to the procedure reported in the literature,[11] by treating *trans*-$[PdX_2(PPr^n_3)_2]$ with PPr^n_3 in EtOH–water. The benzodiazepines, provided by pharmaceutical manufacturers, were used without further purification. Pyridine and 2,6-dimethylpyridine were distilled over KOH pellets. All the solvents used were of spectroscopic grade.

* *Supplementary data available* (No. SUP 56815, 4 pp.): pseudo-first-order rate constants and equilibrium constants. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1991, Issue 1, pp. xviii–xxii.



Scheme 1

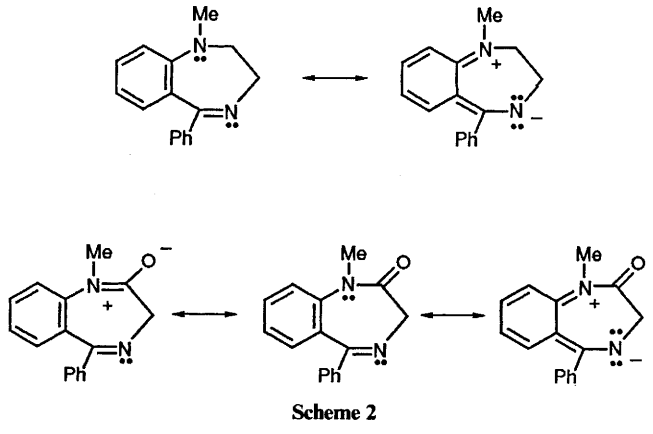
Conductivity experiments were performed with a Radiometer CDM3 conductivity bridge. The electronic spectra were recorded by means of a model 8452A Hewlett-Packard diode-array spectrophotometer or of a Perkin-Elmer Lambda 5 spectrophotometer.

Thermodynamics and Kinetics.—Equilibrium constants for the reaction of $[Pd_2I_4(PPr^n_3)_2]$ with the various benzodiazepines in chloroform were determined spectrophotometrically by use of a Perkin-Elmer Lambda 5 spectrophotometer equipped with a thermostatted cell holder. Solutions of fixed $[Pd_2I_4(PPr^n_3)_2]$ concentration containing different known amounts of benzodiazepine were prepared and their absorbances recorded, at four temperatures, in a 1 cm stoppered silica cell, at a wavelength where the difference in absorbance between the iodide-bridged complex and the adduct with benzodiazepine was as large as possible and the contribution of the benzodiazepine to the total absorption negligible. The temperature was controlled to ± 0.2 °C by means of an electronic thermometer.

The kinetics were performed under pseudo-first-order conditions with respect to the iodide-bridged complex at 25 °C in chloroform. The reaction course was followed spectrophotometrically by using a SFA-11 HI-TECH stopped-flow accessory connected to a model 8452 Hewlett-Packard diode-array spectrophotometer. Pseudo-first-order rate constants were obtained either from the gradients of the plots $\log(A_t - A_\infty)$ *vs.* time or from non-linear least-squares fits of the experimental data by $A_t = A_\infty + (A_o - A_\infty)\exp(-k_{obs}t)$, where A_o, A_∞, and k_{obs} were the parameters optimized (A_o = absorbance after mixing of the reagents, A_∞ = that upon completion of reaction). The k_{obs} values were reproducible to better than $\pm 5\%$.

Results and Discussion

The complexes $[Pd_2X_4(PPr^n_3)_2]$ (X = I or Cl) are promptly cleaved by each of the 1,4-benzodiazepines used in this work to give monomeric complexes in which (Scheme 1) the benzodiazepine occupies the position *trans* to phosphine and is, most likely, co-ordinated through N(4). We have recently isolated [1,8] the adduct between $[Pd_2Cl_4(PPr^n_3)_2]$ and 7,8-dichloro-2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine and shown that both in the solid and in solution the ligand is indeed co-ordinated through the nitrogen atom bound to carbon *via* a double bond. On the other hand in all the complexes of benzodiazepines so far isolated and characterized in the solid by X-ray analysis the benzodiazepine is bound to N(4), unless the ligand is in a deprotonated form. This circumstance, which in our case has been excluded by conductivity measurements in dichloromethane and acetone, may occur in basic media [1,8] or in the presence of free strong bases.[5]



Scheme 2

In chlorinated or hydroxylic solvents the reactions do not go to completion under stoichiometric conditions. Thanks to the large spectral variation associated with the process, the equilibrium constants K in equation (2) could be conveniently

$$K = [PdI_2(PPr^n_3)L]^2/[Pd_2I_4(PPr^n_3)_2][L]^2 \quad (2)$$

obtained by spectrophotometry. Plotting the quantity $[2(1 - \alpha)c_{bridge}]^2/[\alpha c_{bridge}]$ against $[c - 2(1 - \alpha)c_{bridge}]$,[2] where α is the fraction of uncleaved bridged complex, given by $(A_{mixture} - A_{monomer})/(A_{bridge} - A_{monomer})$ and c_{bridge} and c are the analytical concentrations respectively of the bridged complex and of the benzodiazepine, good straight lines with zero intercept were obtained in agreement with the reaction scheme proposed.

The reaction enthalpy was obtained through Van t'Hoff plots of the equilibrium constants, usually determined at four temperatures each differing by ten degrees. The reaction entropies were calculated by the Gibbs Helmoltz equation (3). The values

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (3)$$

of the equilibrium constants in $CHCl_3$, at 25 °C, as well as the thermodynamic parameters associated with the reactions of all the benzodiazepines with the iodide-bridged complex, are reported in Table 1.

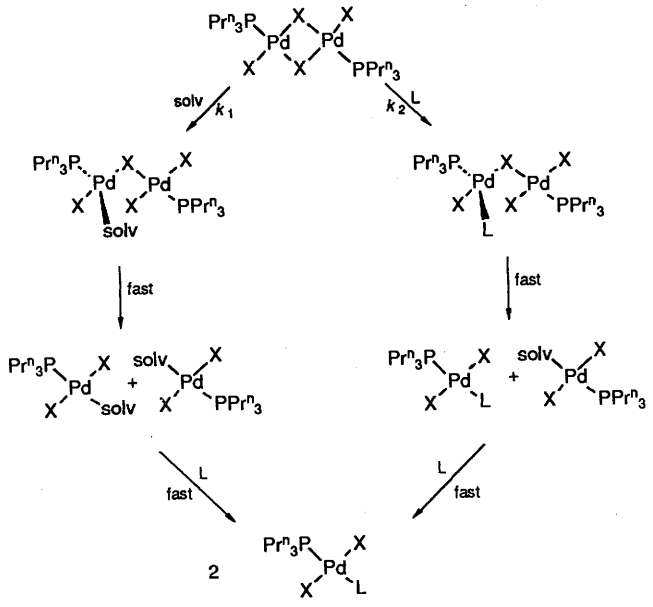
There is a considerable variation in the co-ordinating ability of the various benzodiazepines. The difference between the equilibrium constants for the complexes with bromazepam and medazepam, which are respectively the largest and the smallest, approaches four orders of magnitude. The reactions are exothermic and are all characterized by a large decrease in entropy as expected for processes in which there is a decrease in the number of free particles in solution; in addition the similarity of the ΔS° values shows that the difference in stability of the complexes is to be attributed largely to enthalpic factors. The stability of the complexes with diazepam, clonazepam and nitrazepam is very similar showing that the nature of the substituents at the rings in benzodiazepin-2-ones does not affect significantly their co-ordinating ability. Medazepam gives the strongest complex among those studied; it is significant in this respect that this 1,4-benzodiazepine is the only one not in the 2-keto form. The higher electron density at the donor site in this case can be accounted for by resonance among the three rings as shown in Scheme 2.

Finally, the stability of the complex with bromazepam is lower than that of all the other complexes. Bromazepam is potentially a bidentate ligand and all the complexes of this ligand so far characterized [4,7] are chelated by N(4) and the pyridinic nitrogen. The trend in the thermodynamic data for

Table 1 Equilibrium constants and thermodynamic properties for the reaction $[Pd_2I_4(PPr^n_3)_2] + 2L \longrightarrow 2[PdI_2(PPr^n_3)L]$, L = benzodiazepine

Benzodiazepine	$10^{-3}K_{25}$·c/dm^3 mol^{-1}	ΔG°/kJ mol^{-1}	ΔH°/kJ mol^{-1}	ΔS°/J K^{-1} mol^{-1}
Diazepam	1.19	−17.53	−48.1 ± 1.3	−100 ± 8
Nitrazepam	0.41	−14.94	−42.3 ± 1.7	−92 ± 8
Clonazepam	0.82	−15.76	−44.8 ± 1.3	−92 ± 4
Bromazepam	0.08	−10.96	−45.2 ± 2.5	−113 ± 8
Medazepam	414	−32.05	−59.0 ± 2.9	−92 ± 4
Pyridine	596	−32.93	−63.6 ± 1.7	−105 ± 8
2,6-Dimethylpyridine *	2670	−42.26	−69.4	−92

* Approximate values obtained at two temperatures only.



Scheme 3

the reactions studied, however, excludes the formation of a chelate in the case of bromazepam. Conductometric studies of the reaction between $[Pd_2X_4(PPr^n_3)_2]$ and bromazepam in CH_2Cl_2, a solvent in which the equilibrium position is essentially the same as in $CHCl_3$, are consistent with such an assumption. The absence of a conductivity increase associated with the reaction rules out the release of a halide ion necessitated by chelation. Bromazepam behaves, therefore, like all the other benzodiazepines, as a monodentate ligand. The lower stability of its complex with palladium with respect to the complexes of the other benzodiazepines in 2-keto form is probably due to the presence in this ligand of one additional electronegative atom, the pyridine nitrogen, which shares with the reaction site the electron pairs. It is interesting that on going from chlorinated to hydroxylic solvents, probably because of a better solvation of Cl^-, the reaction of $[Pd_2Cl_4(PPr^n_3)_2]$ with bromazepam exhibits different features. In methanol the spectral changes associated with the process are different than in chloroform or dichloromethane and there is a definite conductivity increase which may well be due to the release of chloride according to equation (4) (L = bromazepam).

$$[Pd_2Cl_4(PPr^n_3)_2] + 2L \longrightarrow 2[PdCl(PPr^n_3)L]^+ + 2Cl^- \quad (4)$$

The thermodynamic data for L = pyridine conform to the general trend observed for the other ligands. In particular the stability of the complex with pyridine is comparable to that with medazepam and this shows that the presence of a bulky benzodiazepine in the complex does not introduce any steric constraint. 2,6-Dimethylpyridine forms a stronger complex than that with pyridine as a result of the presence of the two methyl groups which increase the electron density on the donor atom. The entropy of reaction is in the range of those for the other ligands although, in this case, the equilibrium position lies too far to the right to allow a good determination of thermodynamic parameters.

The kinetics of cleavage of halide bridged complexes of palladium(II), probably because of their high lability, has seldom been studied.[12] Preliminary kinetic experiments have shown that the rate of cleavage of $[Pd_2Cl_4(PPr^n_3)_2]$ by the common nucleophiles in various solvents, at room temperature, are too fast to follow by the stopped-flow technique. Nonetheless because of the large difference in lability between the chloro and the iodo complex we could study conveniently the rate of the reaction between $[Pd_2I_4(PPr^n_3)_2]$ and our 1,4-benzodiazepines, in chloroform at 25 °C. Using a large excess of nucleophile with respect to the complex, both to reach pseudo-first-order conditions and to avoid the reverse reaction, a simple rate equation (5) was obeyed. The term k_1 was much smaller than k_2 but could be evaluated in most cases.

$$k_{obs} = k_1 + k_2[L] \quad (5)$$

Our kinetic data can reasonably be interpreted in the light of the mechanism depicted in Scheme 3 originally proposed by Pearson and Muir.[12] According to this scheme the reaction proceeds through two parallel paths one involving the nucleophile and the other the solvent (solv). In a first step, which is rate determining, both the solvent and the nucleophile attack the metal giving rise to a monobridged species and in subsequent fast steps the second bridge is broken and the final product forms; k_1 represents the rate constant corresponding to the attack of the solvent at the metal and k_2 the second-order rate constant referring to the direct attack of the nucleophile. Therefore, for a series of reactions involving a given substrate, in a fixed solvent, and various nucleophiles the k_1 term should be constant, while k_2 should vary as a function of the nature of the nucleophile. The term k_1 was somewhat sensitive to the type of chloroform used, probably because water and methanol, inevitably present as impurities, rather than chloroform itself determine the k_1 value. Our data (Table 2) have therefore been obtained using the same stock of solvent, and show that the k_1 value, when obtainable, is reasonably constant throughout the series of reactions. The second-order rate constants k_2 show a dependence on the benzodiazepine nature although this dependence is rather small. In this respect one should not forget that the donor atom throughout the series of ligands is the same and that the micropolarizability of the nucleophile, *i.e.* its polarizability in the anisotropic electric field encountered in the transition state,[13] which is the most important factor in determining the reactivity, should be essentially the same in all cases. It is interesting that the reactivity of these ligands is about three orders of magnitude lower than that of pyridine, which is in turn a very poor nucleophile toward platinum(II)[14] and palladium(II).[15] Such a low nucleophilicity is attributed to *steric* rather than to electronic reasons, probably because the phenyl ring adjacent to the donor atom hampers the approach of the

Table 2 First- and second-order rate constants for bridge cleavage of $[Pd_2I_4(PPr^n_3)_2]$ by various 1,4-benzodiazepines and rate constants for the reverse reactions in $CHCl_3$ at 25 °C

Benzodiazepine	$10^3 k_1/s^{-1}$	$k_2/dm^3\ mol^{-1}\ s^{-1}$	$10^{-2}\ k_r*/s^{-1}$
Diazepam	51 ± 2	25.3 ± 0.3	2.13
Nitrazepam	52 ± 5	34.4 ± 1.2	8.39
Clonazepam	52 ± 9	64.0 ± 0.9	7.80
Bromazepam	46 ± 1	25.9 ± 0.1	32.4
Medazepam		124 ± 1	0.03
Pyridine		36 693 ± 1 123	
2,6-Dimethylpyridine	46.2 ± 1	26.5 ± 0.4	

* Data obtained from the ratio k_2/K.

nucleophile to the metal for the formation of the activated complex; in fact the reactivity of the various benzodiazepines is similar to that of 2,6-dimethylpyridine. This ligand, which bears two methyl groups in α position with respect to the pyridinic nitrogen, is known to be a much poorer nucleophile than pyridine or pyridines substituted in positions other than 2 or 6 toward square-planar complexes, for steric reasons.[16]

On the basis of the similarity of the kinetic values for the various benzodiazepines, the difference in stability of their complexes with palladium(II) can be accounted for in terms of variations of the rate constants k_r for the reverse reactions, *i.e.* the release of the co-ordinated benzodiazepines. The values of k_r derived from the ratio k_2/K are reported in Table 2 and indicate that benzodiazepines forming weak complexes are released faster than those forming strong ones. In conclusion these 1,4-benzodiazepines form complexes of considerably different stability; when the ligands are in the 2-keto form the resulting complexes are much weaker. The rates of cleavage of $[Pd_2I_4(PPr^n_3)_2]$ by the various benzodiazepines, *i.e.* their nucleophilic reactivities toward palladium(II), which, for steric reasons, are very low in comparison with other nucleophiles, are similar suggesting a reverse relationship between Pd–N bond strength and the rate of dissociation of the benzodiazepine ligand.

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